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Title:

Late presentation of acute hypercapnic respiratory failure carries a high mortality risk in COPD patients treated with ward-based NIV

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Abstract

Introduction: Non-invasive ventilation (NIV) is recommended for treatment of acute hypercapnic respiratory failure (AHRF) refractory to medical management in patients with COPD. This study investigated the relationship between time from hospital presentation to diagnosis of AHRF and in-hospital mortality.

Methods: Retrospective analysis of hospitalised COPD patients treated with a first episode of ward-based NIV for AHRF at a large UK teaching hospital between 2004 and 2017. Data collected prospectively as part of NIV service evaluation. Multivariable logistic regression performed to identify predictors of in-hospital mortality.

Results: In total, 547 unique patients were studied comprising 245 males (44.8%), median age 70.6 years, median FEV1 % predicted 34%. Overall in-hospital mortality was 19% (n=104); median survival was 1.7 years. In univariate analysis, a longer time between hospital presentation to diagnosis of AHRF was associated with in-hospital mortality (median [IQR]: 8.7 [0.7-75.8] hours vs. 1.9 [0.3-13.6] hours, p<0.0001). In multivariable logistic regression, significant predictors of in-hospital mortality were AHRF >24 hours after hospital presentation (odds ratio [95% CI]: 2.29 [1.33-3.95], p=0.003), pneumonia on admission (1.81 [1.07-3.08], p=0.027), increased age (1.10 [1.07-1.14], p<0.001) and NIV as ceiling of treatment (5.86 [2.87- 11.94], p<0.001).

Conclusions: Hospitalised COPD patients with late presentation of AHRF, requiring acute ward-based NIV, may have increased in-hospital mortality. These patients may benefit from closer monitoring and earlier specialist respiratory review.

Keywords: chronic obstructive pulmonary disease; acute exacerbation; ward-based; non-invasive ventilation; acute hypercapnic respiratory failure; mortality.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common respiratory conditions in the UK and the third leading cause of death worldwide [1-3]. Acute exacerbations of COPD (AECOPD) are common and a significant year-on-year increase in the rate of AECOPD has been seen in England [4]. Acute hypercapnic respiratory failure (AHRF) is a recognised complication in AECOPD and occurs in approximately 20% of hospitalised cases [5, 6]. Crucially, development of AHRF is associated with worse clinical outcomes including increased in-hospital mortality and post-discharge mortality [5, 7].

Medical management of AHRF in AECOPD includes targeting oxygen saturation to 88-92% and administering intra-venous fluids, bronchodilators, steroids and antibiotics if clinically indicated [8-10]. Non-invasive ventilation (NIV) is recommended for the treatment of AHRF when, following >60 minutes of optimal medical management, the following criteria are met: pH <7.35 and arterial pCO2 > 6.5 kPa [11, 12]. A recent systematic review and meta-analysis of randomised controlled trials found that use of NIV for the management of AHRF in AECOPD was associated with reductions in the risk of mortality and endotracheal intubation of 46% and 65% respectively [13].

The survival benefits associated with NIV seen in 'real life' data obtained by the UK National COPD Resources and Outcomes Project (NCROP), British Thoracic Society (BTS) adult NIV audits and the National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) have been less striking [6, 14, 15]. Of concern, there appears to be a group of patients with AECOPD who are admitted without AHRF but go on to develop AHRF later during their hospital admission. These patients have been reported to be at risk of worse outcomes, however the literature describing this group is limited. This study aimed to evaluate the relationship between time from hospital presentation to diagnosis of AHRF and in-hospital mortality in COPD patients treated with ward-based NIV.

Methods

Study population

This was a single centre, retrospective, observational cohort study. Patients with COPD undergoing a first episode of ward-based NIV for AHRF at a large teaching hospital in the West Midlands (UK) were prospectively enrolled into the NIV department registry between July 2004 to November 2017. The NIV service is run in a dedicated bay on a respiratory ward, with an acuity-based nursing staffing level scoring system (supplementary material section A), and daily senior specialist respiratory ward rounds, as well as a 7 day physiotherapy support service. Clinical diagnoses of COPD were confirmed with spirometry (FEV_1/FVC ratio <0.7). In patients without spirometry, discharge letters, respiratory clinic letters, chest x-rays and computed tomography (CT) findings were reviewed to verify clinical diagnoses. Patients were selected for acute, ward-based NIV as per Trust protocol (supplementary material section B).

Data collection

A diagnosis of pneumonia was made by the attending clinician at the time of admission and was confirmed by chest x-rays review by a member of the research team. CT scans were reviewed for evidence of bronchiectasis. Arrival times at the emergency department (ED) were extracted from electronic records. Pre-NIV arterial blood gas results and time of AHRF diagnosis were identified from case notes and recorded prospectively by NIV physiotherapists. The primary outcome of interest was in-hospital mortality.

Statistical analysis

Data were analysed in STATA version 15 (StataCorp, Texas, USA). Non-parametric data were expressed as median [inter-quartile range] and were analysed using the Mann-Whitney U test. Categorical data were expressed as number (percentage) and were analysed using the Chi-Squared test. A p-value <0.05 was considered statistically significant. Prognostic variables that were statistically significant in univariate analysis were taken forward into a multivariable logistic regression model to identify predictors of in-hospital mortality. A cut-off value of 24 hours from

arrival in the ED to diagnosis of AHRF was used to dichotomise patients to enable comparison with the NCEPOD data [15]. Kaplan Meier curves were constructed to compare in-hospital mortality in patients with or without pneumonia and in patients stratified by length of time between hospital presentation to diagnosis of AHRF (≤24 hours vs. >24 hours).

Results

A total of 829 eligible NIV admissions secondary to AHRF were available with 153 patients being admitted multiple times during the study period. Ninety three patients (61%) were admitted twice and with the remainder admitted between 2 and 10 times with only 7% admitted more than 5 times over the study period (supplementary material section C). There were 547 unique patients who attended as first presentation for NIV with 104 (19%) experiencing in-hospital mortality. Characteristics of the study population are summarised in Table 1. Median survival following first admission for acute ward-based NIV was 1.7 [1.4-2.03] years (supplementary material section D). Survivor functions were calculated at predetermined timepoints to give an estimate of 1-year, 3-year and 5-year survival. One-year survival in this cohort was 58.6% [54.3-62.7%], 3-year survival was 33.8% [29.5-38.1%] and 5-year survival was 22.3% [18.1-26.6%].

Table 1. Participant characteristics split by primary endpoint (in-hospital mortality).

	Median [IQR] or n (%)			
Characteristic	**Total (n=547)**	**Died in hospital (n=104)**	**Discharged (n=443)**	**P value**
Age (years)	70.6 [63.78-78.13]	79.56 [71.89-84.69]	69.45 [62.5-75.61]	<0.0001
Male gender	245 (44.79)	44 (42.31)	201 (45.37)	0.572
Pneumonia on admission	143 (27.66)	42 (42.86)	101 (24.11)	<0.0001
Bronchiectasis#	104 (26.4)	19 (26.39)	85 (26.4)	0.999
FEV_1 (litres)*	0.71 [0.54-0.96]	0.7 [0.5-0.9]	0.72 [0.55-0.98]	0.349
FEV_1 % predicted*	34 [26-43]	34 [27-46]	34 [25.55-43]	0.3501
NIV ceiling of treatment	301 (55.03)	92 (88.46)	209 (47.18)	<0.0001
Pre-NIV pH	7.27 [7.21-7.3]	7.26 [7.2-7.3]	7.27 [7.22-7.31]	0.2065
Pre-NIV pCO2 (kPa)	9.91 [8.43-11.5]	10.1 [8.56-11.8]	9.86 [8.4-11.4]	0.34
Pre-NIV pO2 (kPa)	7.83 [6.73-9.49]	7.74 [6.67-9.3]	7.85 [6.74-9.51]	0.3809
Arrival to AHRF (hours)	2.17 [0.32-19.93]	8.67 [0.69-75.83]	1.87 [0.25-13.58]	<0.0001
Arrival to AHRF >24 hours	124 (22.67)	41 (39.42)	83 (18.74)	<0.0001
AHRF to NIV (hours)	1.83 [1-3.67]	1.67 [1-3.6]	1.87 [0.25-13.58]	0.5204
Duration of NIV (days)	5.07 [3.04-7.1]	3.04 [1.01-6.09]	5.07 [3.04-7.1]	0.0002
Maximum IPAP (cmH_2O)	16 [14-20]	17 [14-20]	16 [14-20]	0.1312

Maximum EPAP (cmH_2O)	5 [4-6]	5 [4-6]	5 [4-6]	0.6958
Maximum oxygen (litres/min)	5 [3-10]	7 [4-12]	5 [3-10]	0.0023
Transferred to ICU	17 (3.11)	4 (3.85)	13 (2.93)	0.630
Intubated	10 (1.83)	4 (3.85)	6 (1.36)	0.089

Abbreviations: CT, computed tomography; FEV_1, forced expiratory volume in one second; NIV, non-invasive ventilation; Arrival to AHRF, time from presentation to the emergency department to diagnosis of AHRF; AHRF to NIV, time from diagnosis of AHRF to application of NIV; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; ICU, intensive care unit. #Bronchiectasis based on a total of 394 patients with either CT available (n=338) or clinical diagnosis from patient records (n=56), *FEV_1 based on 419 patients with available spirometry.

In univariate analysis, a longer time between hospital presentation to diagnosis of AHRF was associated with in-hospital mortality (8.7 [0.7-75.8] vs. 1.9 [0.3-13.6] hours, p<0.0001) and a higher proportion of patients with in-hospital mortality were diagnosed with AHRF >24 hours after presentation to hospital (41 [39.4%] vs. 83 [18.7%], p<0.0001). Long term median survival for those diagnosed with AHRF<24 hours post admission compared to AHRF>24 hours post admission differed (1.7 [95%CI 1.47-2.16] vs. 0.84 [95%CI 0.28-1.92] years, p=0.046).

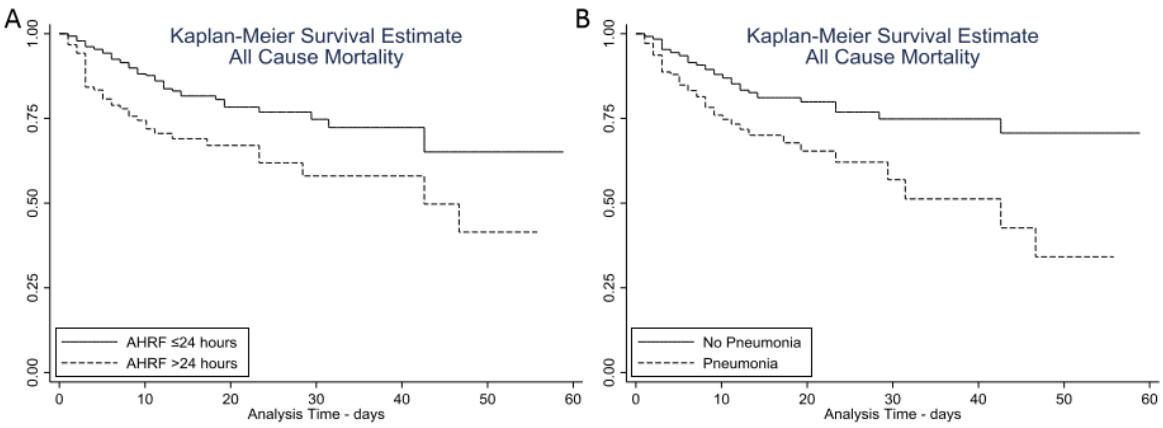
Patients with in-hospital mortality were also older (79.6 [71.9-84.7] vs. 69.5 [62.5-75.6] years, p<0.0001), had a higher rate of pneumonia on admission chest x-ray (42 [42.9%] vs. 101 [24.1%], p<0.0001), higher proportion with NIV as a ceiling of treatment (92 [88] [74%] vs. 209 [47%], p<0.0001), shorter duration of NIV (3.04 [1.01-6.09] days vs. 5.07 [3.04-7.1] days, p=0.0002) and a higher maximum oxygen flow during NIV (7 [4-12] L/min vs. 5 [3-10] L/min, p=0.0023). They also had a shorter duration of NIV (3.04 [1.01-6.09] days v's 5.07 [3.04-7.1] days, p=0.0002) .There were no differences between groups in gender, rate of co-morbid bronchiectasis, FEV_1, pre-NIV arterial blood gas result, time from diagnosis of AHRF to application of NIV, rate of transfer to ICU, intubation rate or maximum IPAP or EPAP achieved during NIV.

In multivariable logistic regression, significant predictors of in-hospital mortality were AHRF >24 hours after hospital presentation, pneumonia on admission, increased age and NIV as ceiling of treatment (Table 2). Kaplan Meier curves were constructed comparing in-hospital mortality in groups split by AHRF >24 hours after hospital presentation and pneumonia on admission (Figure 1).

Table 2. Multivariable logistic regression.

Variable	Odds Ratio	Standard Error	95% Confidence Interval		P-value
			Lower	Upper	
Arrival to AHRF >24 hours	2.29	0.64	1.33	3.95	p=0.003
Pneumonia on admission	1.81	0.49	1.07	3.08	p=0.027
Increased age	1.10	0.02	1.07	1.14	p<0.001
NIV ceiling of treatment	5.86	2.13	2.87	11.94	p<0.001

Figure 1. Kaplan Meier curves illustrating in-hospital mortality in patients stratified by AHRF >24 hours after hospital presentation (A, log-rank: p=0.0001) and pneumonia on admission (B, log-rank: p=0.0002).



Discussion

This study of COPD patients undergoing a first episode of acute ward-based NIV found that patients who presented with AHRF later during hospital admission experienced increased in-hospital mortality. This relationship persisted after adjustment for confounding factors in a multivariable model and remained the most significant independent predictor of in-hospital mortality. The inclusion of only patients at first presentation is due to the differences that have been identified previously in the literature and specifically in this cohort. This has including the more rapid progression from ED onto the NIV service of those who are on the second or later presentation, which presumably occurs due to their pre-identified risk factor of prior NIV, and proven previous efficacy of NIV treatment [16].

Prognostication in AECOPD is an important and evolving area [17]. The high mortality rate experienced by patients with AHRF necessitates careful identification of factors that predict poor outcome. NCEPOD found that patients initiated on NIV 24 hours after admission had greater in-hospital mortality (55.6% vs. 25.1%). Prior to this, Roberts et al. [6] presented a large UK dataset of hospitalised COPD patients, of which 1077 patients had received acute NIV. The authors split patients into three groups, with different mortality rates, based on timing of acidosis: lowest pH on admission, acidotic on admission but a lower pH later and non-acidotic on admission but acidotic later (in-hospital mortality rates: 19% vs. 26% vs. 39%, respectively). Our findings are therefore in-keeping with the data from Roberts et al. [6] and NCEPOD [15] but go further in describing the relationship between the timing of AHRF and risk of in-hospital mortality. In this study, we were able to ascertain independent predictors of in-hospital mortality by way of detailed individual patient data, enabling us to quantify the relationship between timing of AHRF and mortality.

Reasons for later development of AHRF in COPD patients presenting to the ED are likely to be multifactorial. It is feasible that later diagnosis of AHRF may reflect a lack of patient response to initial medical treatment, indicating more severe acute illness. The inappropriate use of and control of supplementary oxygen in COPD has also been cited previously [18, 19]. A competing mechanism

would be that these patients represent a phenotype of AECOPD patients who, as part of the course of their disease, deteriorate later. These patients may represent a frail subgroup of patients, whom need careful monitoring and earlier input from respiratory specialists [20, 21]. It is possible that later development of acidosis may, in part, result from concurrent metabolic acidosis, due to competing pathophysiological mechanisms including acute kidney injury and hypovolaemic hypoperfusion of tissues. However, this mechanism would not warrant use of NIV as a treatment for acidosis, hence is less likely in our cohort where detailed case note review was able to adequately exclude this.

Concerningly, a large proportion of patients in our cohort had concomitant pneumonia on admission chest x-ray and these patients had higher in-hospital mortality. This finding is in-keeping with the NCEPOD data which found that patients with pneumonia had higher in-hospital mortality (44.4% vs. 24.8%). It is important to note that, in our study, >50% of patients had NIV as a ceiling of treatment. This may partly explain the high proportion of patients with concomitant pneumonia being treated with ward-based NIV, rather than being transferred to critical care. Moreover, a significantly higher proportion of patients who died in hospital had NIV as a ceiling of treatment (88% vs. 47%, $p<0.0001$). Those patients that died whilst in hospital were on NIV for a shorter period of time possibly reflecting more rapid clinical deterioration or poor tolerance of the treatment, with few other options available, and a shift to palliation. The latter is consistent with the high number of patients that were given NIV as a ceiling of treatment due to clinician's perceptions about survival and futility of care. Further exploration of the impact of attitudes to commencing NIV and subsequent case management including palliative care, would require a prospective design with a mixed methods approach focussed on clinical decision making. Attitudes toward death, and a feeling that 'something must be tried' even if it is likely to be futile may well be playing a part.

The finding that very few patients were transferred to the ICU or were intubated, is in-keeping with national data [14]. As discussed, this may simply reflect a higher proportion of patients having NIV as a ceiling of treatment, however this may also reflect increased confidence and competence in the delivery of acute ward-based NIV, obtained over the past two decades [22]. A recent model of care

and economic assessment between differing settings (ward based, high dependency unit and ICU) for the provision of NIV in treating AHRF demonstrated the ward environment produced equivalent clinical outcomes at a lower cost per patient [23] again supporting the delivery of service in this environment.

The higher mortality rate seen in patients with concomitant pneumonia highlights the importance of the NCEPOD recommendation that "Early senior review and escalation planning is essential to ensure these patients receive appropriate treatment in the correct location."[15]. Carlucci et al [24] highlight important changes in the presentation and severity of patients requiring NIV over an 8 year period and it is accepted that this observational study was undertaken over a prolonged period of time, 2004-2017. Previously published data by Trethewey et al [25] compared two cohorts of patients between 2004-2010 and 2013-2017 and observed patients with more severe presentations of AHRF, yet stable in-hospital mortality, alongside a decline in the duration of NIV treatment and hospital length of stay for survivors implying that this may be a factor in our cohort. To address this we conducted a sensitivity analysis in which an extra variable of 'admission year' was added to the model (supplementary material section E); this suggested that year of admission for NIV did not impact the odds ratio for in-hospital mortality in this cohort or offer improvement to the fit of the model.

The global burden of COPD is high and appears to be increasing [2]. Importantly, as part of the natural course of the disease, a significant proportion of patients will experience an AECOPD [26]. A key finding from the landmark Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study was that, during 3-year follow-up, 31% of patients experienced at least one AECOPD requiring hospital admission [27]. Crucially, around 20% of hospitalised patients with AECOPD will develop AHRF and this is associated with a significant mortality rate [5, 6]. The overall in-hospital mortality rate of 19% observed in our cohort is higher than in the original randomised controlled trial advocating the use of NIV in AECOPD [28] but markedly lower than the data presented by NCEPOD (25.1%) and NCROP (25%) [6, 15]. It is possible that the lower overall mortality seen in our cohort may, in part, be due to the early adoption and development of an acute,

ward-based NIV service and implementation of BTS-recommended NIV leadership at our institution [29, 30]. However, it is important to note that median survival in this patient cohort was poor, which is in-keeping with data from a recent, large, retrospective observational cohort study of COPD patients aged ≥65 years, derived from a US Medicare database by Lindenauer et al. [7]. The authors observed a 1-year mortality rate of 41.8% in COPD patients who survived to hospital discharge following admission for acute NIV between 2008-2014. Taken together, these findings highlight the poor long-term prognosis in COPD patients treated with acute NIV. Survivors of acute NIV should therefore have future treatment plans discussed and documented, including advance-care planning and patient preferences regarding emergency care decisions in the likely event of future clinical deterioration. Despite international consensus regarding the importance of advance-care planning in patients with severe COPD, barriers to this process persist [31]. A qualitative study by Smith et al. [32] demonstrated that although many survivors of acute NIV have contemplated their mortality and preferences regarding future treatment and resuscitation decisions, many do not discuss these preferences with healthcare professionals. Further research regarding optimal methods and timing of advance-care planning discussions is needed to improve this important aspect of care in survivors of acute NIV.

Strengths and Limitations:

Key strengths of this study include the large cohort size, which is significantly larger that the COPD cohort analysed as part of the NCEPOD report. Additional strengths of this study include the long observation period and the reliability of clinical diagnoses of COPD utilising spirometry, CT findings, chest x-ray reports, clinical letters and discharge summaries. The findings of this study are limited by the uncontrolled, retrospective observational cohort design. Reporting of initial ‘arrival in ED’ times relied on electronic input of data by triaging clinicians, which may be subject to inaccuracy. We were unable to replicate data by Roberts et al [6] in reporting rates of ABG’s performed at the first point of care in ED. Whilst this study cannot rule out a delay in an appropriate and timely ABG on admission to ED, COPD patients admitted to our ED would normally have ABG done as an initial triage

screening that would be expected to have been completed within 4 hours of documented admission. A prospective, observational cohort study, with serial ABGs, is required to confirm these findings.

Whilst chest x-ray review was undertaken for confirmation of a pneumonia diagnosis these were not further classified (eg lobar, diffuse) in the scope of this work. A future research plan is to review and classify these and review any associated microbiology results available. It is accepted that patient BMI may affect the success of NIV, however this was not reliably recorded in the clinical case notes and therefore is a limitation of this study.

Conclusions:

In summary, hospitalised COPD patients with late presentation of AHRF, requiring acute ward-based NIV, may have increased in-hospital mortality. These patients may benefit from closer monitoring and earlier specialist respiratory review. Further research is required to elucidate clinically relevant time points and their relationship with mortality and highlight deficiencies in the timeliness of clinical diagnostic testing to inform clinical decision making.

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Author contributions:

AMT and RM designed the study, assisted with data collection and interpretation, revised the manuscript and approved the final version for submission. SPT assisted with data collection, analysis and interpretation, drafted the manuscript and approved the final version for submission. RGE and JM assisted with data analysis and interpretation, revised the manuscript and approved the final version for submission.

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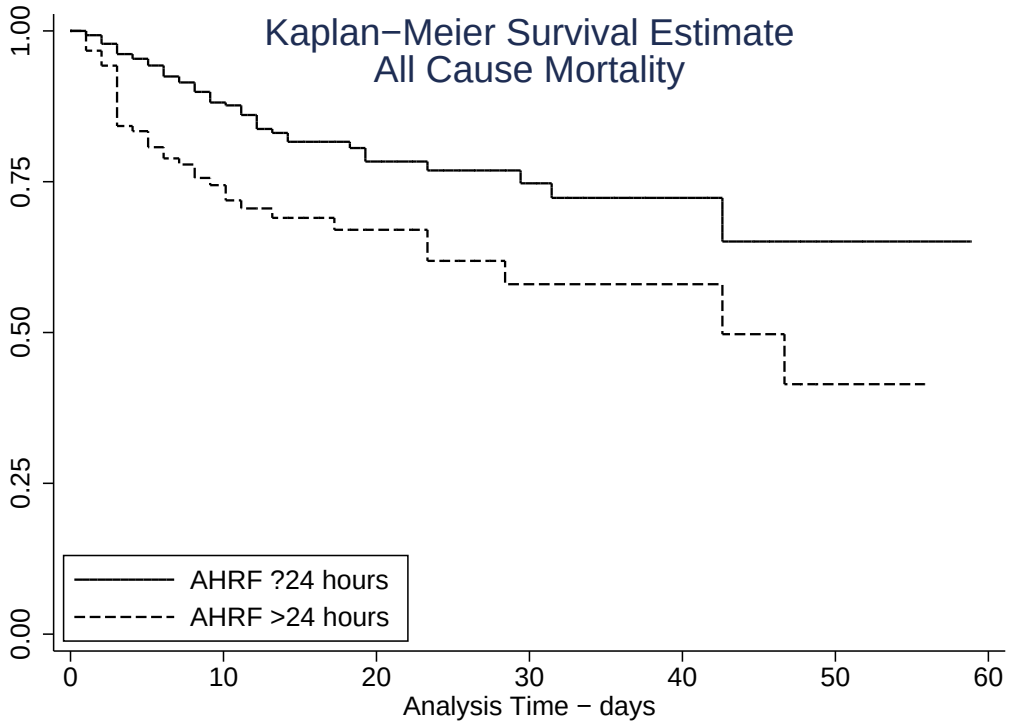

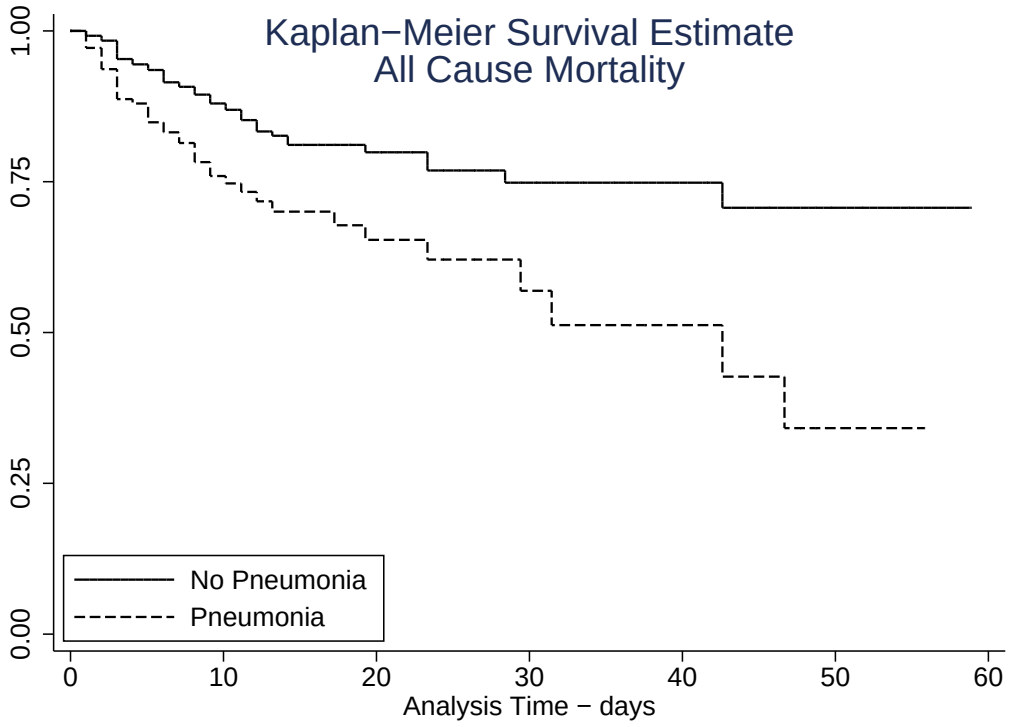

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Late presentation of acute hypercapnic respiratory failure carries a high mortality risk in COPD patients treated with ward-based NIV

- Increased in-hospital mortality in COPD patients with AHRF >24 hours post admission
- >50% of patients started on ward-based NIV had this as ceiling of care
- Pneumonia presents increased odds of in-hospital mortality with ward-based NIV

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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